Identification of i(X)(p10) as the sole molecular abnormality in atypical chronic myeloid leukemia evolved into acute myeloid leukemia

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Abstract. The World Health Organization classifies atypical chronic myeloid leukemia (aCML) as a myeloproliferative/myelodisplastic hematological disorder. The primary manifestations are leukocytosis with disgranulopoiesis, absence of basophilia and/or monocytosis, splenomegaly and absence of Philadelphia chromosome or BCR/ABL fusion. Overall 50-65% of patients demonstrate karyotypic abnormalities, although no specific cytogenetic alterations have been associated with this disease. X chromosome alterations have been rarely reported in myeloid malignancies. Although Isodicentric X, idic(X)(q13) is well known in females with myelodysplastic syndromes (MDS), little data are available on X isochromosome and its pathogenetic potential in these disorders. i(X)(p10) is observed in a variety of hematologic malignancies, both myeloid and lymphoid, as a unique abnormality, as well as part of a more complex karyotype, in females and less frequently in male patients. The present report describes the first patient with aCML, with documented isolated i(X)(p10), who developed a secondary acute myeloid leukemia (sAML).

Case report

A 66 year-old woman presented to the Emergency Room of Tor Vergata University Hospital with lower back pain. Her past medical history was negative. Blood counts (CBC) revealed leukocytosis (55 10^9/l; differential: 87% neutrophils, 5.4% lymphocytes, 6.8% monocytes) and anemia (10 gr/dl). Splenomegaly was present at physical examination (18 cm longitudinal diameter at the abdomen ultrasound). The peripheral blood smear showed presence of immature granulocytes (>10% promyelocytes, myelocytes and metamyelocytes) and 6% myeloblasts, in the absence of monocytosis.

Bone marrow (BM) smears and BM biopsy were hypercellular with left shift of the granulocyte maturation curve, less than 5% $CD34^+$ blasts, dyserythropoiesis and presence of small hypolobated megakaryocytes. Molecular analysis for the BCR-ABL fusion gene (p210, p190, p230), as well as locus-specific FISH for t(9;22) were negative. The standard karyotype analysis gave the initial result of a Xq23 deletion. To better characterize the molecular lesion, array CGH, and a locus-specific FISH were performed, as well as mutation studies on the diagnostic BM sample (Fig. 1 and Table I). The only detectable clonality marker was a X isochromosome i(X)(p10) in 7 of the 15 metaphases analyzed. The diagnosis of aCML was made.

The patient started 5-hydroxyurea (1 g per day), with modest control on leucocytosis. Five months after the primary diagnosis, the patient presented with left hypochondrium pain. A CT-scan was diagnostic for a spleen infarction, with intracapsular hematoma. Thus, she underwent urgent splenectomy. The hystopatological examination of the spleen showed 5% MPO^+ and $CD34^+$ cells with hematopoietic invasion.

Almost one year after the primary diagnosis, exacerbation of leukocytosis (≥100x10^9/l), anemia and thrombocytopenia were observed, and the patient became transfusion-dependent. The BM examination showed leukemic evolution of aCML, with the presence of giant myeloid granular blasts (30% M2 FAB subtype), erythroid dysplasia and absence of megakariocytes. Immunophenotyping confirmed the progression to sAML.

Cytogenetic and molecular studies for recurrent mutations confirmed i(X)(p10) as the sole abnormality.

Discussion

We report on a patient with aCML and a i(X)(p10) as the sole molecular abnormality. Little is known on the mechanism of

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Table I. Somatic mutations studied on the diagnostic BM sample by Sanger sequencing.

Gene locus	Mutation status
IDH1 R132	WT
IDH2 R140	WT
IDH2 R172	WT
DNMT3A R882	WT
SRSF2 P95-96	WT
SF3B1 exons 13-16	WT
U2AF1	WT
SETBP1	WT
ASXL1	*Silent mutation S1253S; 3'UTR A/G, position Chr20:32437360*
ETNK1 exon 3	WT

WT, wild-type.

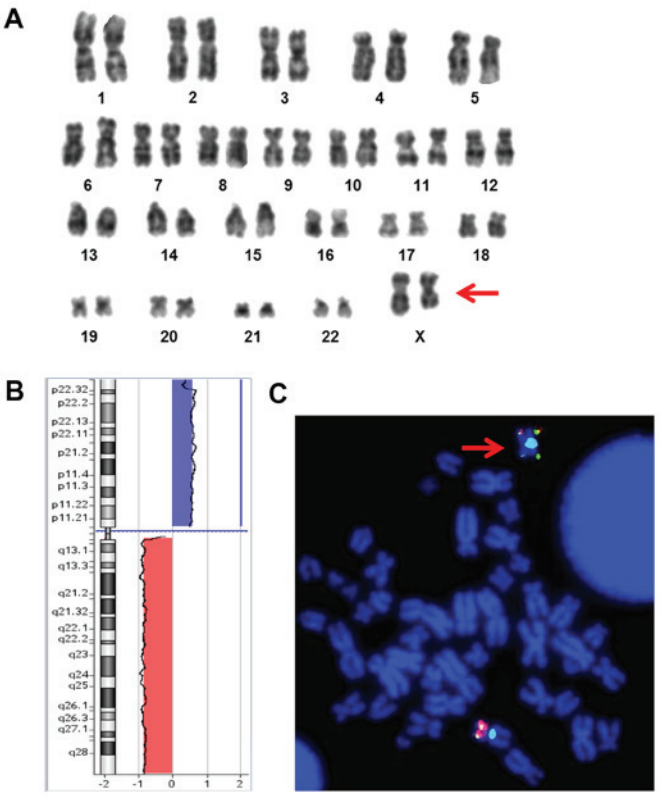

Figure 1. (A) GTG-banded karyotype from cultured bone marrow of the patient showing a del(X)(q23) in ~47% (7/15) of the metaphases analyzed. (B) X chromosome Array-CGH (oligo 180K; Agilent Technologies, Santa Clara, CA, USA) profile showing one duplication of the short arm at Xp22.33q11.1 (blue bar), 62,2 Mb in size and one deletion of the long arm at Xq11.1q28 (red bar), 92,7 Mb in size. (C) FISH analysis, using subtelomeric probes (Abbott Molecular, Des Plaines, IL, USA) specific for chromosome Xpter and Xqter, showing and confirming an isochromosome Xp (red arrow).

isochromosome formation and its pathogenetic impact (1). Frequency varies in different cancers types, with the highest incidence in germ cell neoplasms (60%), and the lowest in chronic myeloproliferative disorders (2.3%) (1).

Isochromosomes could result from transverse, instead of longitudinal meiotic mis-division of the centromere; another mechanism could be chromatid exchange involving two homologous chromosomes. In both cases, it leads to loss and gain of genetic material, likely resulting in deletion of tumor suppressor genes and amplification of oncogenes (2).

Of note, in hematologic neoplasms isochromosome formation is more frequent in lymphoid disorders (three times as common), while in myeloid neoplasms the highest incidence is observed in CML (18%) (2). In particular, i(X)(p10) isochromosome has been described as the sole abnormality in 11 patients, mostly in myeloid neoplasms (4 MDS, 3 AML, 2 chronic myelomonocytic leukemia) while in lymphoid malignancies is usually part of a complex karyotype and seems to be a secondary event (3,4).

The pathogenetic importance of i(X)(p10) is underscored by its presence as the sole acquired abnormality in these disorders. Its formation leads to the loss of the long-arm and gain of short-arm of chromosome X, resulting in a state of genetic imbalance. Costitutional i(X)(p10) is incompatible with life (2). Since i(X)(p10) is found also in males with hematologic disorders, it may reasonably arise from the active X chromosome. Thus, its formation in females may randomly derive from both the active or inactive X chromosome (4).

To the best of our knowledge, this is the first case of i(X)(p10) in aCML. Werner-Favre *et al* described in 1985 a case of aCML carrying a structural rearrangement of X chromosome, del (X)(q23) (5). The cytogenetic distinction between del(Xq) and i(Xp) is known to be difficult due to the similarity of X p- and q-arm band pattern, extending from the centromere to band Xq24 (6). Thus, it is not clear whether the previosuly reported case could be a i(Xp), due to the lack of data from advanced cytogenetic techniques as locus-specific FISH and CGH-array, not available at that time (Fig. 1).

Deletion of the long arm of X chromosome has been reported as recurrent karyotypic abnormality in patients with AML or MDS as well as with solid tumors. Previously, two patients with AML and three with MDS, and del (X)(q23) had been described (7,8). In these cases, only conventional G-banding and dual-color FISH had been performed to rule out the presence of a iso-dicentric (X)(q13). Of note all these patients were females between 46 and 65 years old, with breakpoints regions apparently restricted to q13~q24. The median time to AML progression reported by Olshanskaya for MDS patients was 19 months with a prevalence of FAB M2 AML subtype.

In conclusion, our case highlights the importance of using X p-arm FISH probes to characterize abnormal karyotypes with structural abnormalities of the X chromosome. Furthermore, these results, together with the previously reported i(Xp) and Xq-, indicate that genetic imbalance resulting haploinsufficiency of genes located on the long arm of the X chromosome could drive neoplastic transformation. Of note, the prevalence in females, aged between 46 and 65 years, the myeloid phenotype, and the poor prognosis of all these cases indicate the need for specific molecular biology studies to better characterize the genetic lesions on

the X chromosome, and the putative genes involved in the leukemic evolution.

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